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Evidence of Harmful Health Effects of Occupational Asbestos Exposure

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A retrospective examination of medical histories, clinical and laboratory data of shipyard workers was performed. The study included 170 asbestos-exposed male subjects without asbestosis and 390 asbestos-exposed male subjects with asbestosis. The majority of workers developed asbestosis due to inhalation of asbestos dust and had been exposed to relatively high dust concentrations for a prolonged period. However, many workers who were equally exposed remained healthy. This paper summarises recent studies undertaken to identify and define the differences within an exposed population, with and without occupational asbestosis. The statistical significance with regard to age and duration of exposure, of two and three years, respectively, were not considered biologically significant. Some subjective problems such as cough, heavy breathing, tiredness, sweating and chest pains were found to be associated with the occurrence of asbestosis ($p<0.05$). The risk of asbestosis was greater in smokers than in non-smokers ($p<0.001$). Asbestos bodies and siderophages in sputum indicated past exposure to asbestos dust. Between the diseased and non-diseased workers a significant increase in erythrocyte sedimentation rate was found, and a decreased percentage of segmented leucocytes and increased number of monocytes in the peripheral blood. Significant hypergammaglobulinemia and elevation of serum immunoglobulin levels was also found. The local effect of inhaled asbestos is reflected in the systemic physiology of the diseased group of workers.

A 59

Investigation on the Biodurability of Different Man-Made Mineral Fibres

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In this study the clearance kinetics of different types of man-made mineral fibres was investigated, for which carcinogenicity tests were performed previously. The hypothesis to be tested is that the biodurability correlates with the carcinogenic potency of a fibre type.

Different types of glass microfibres and sized samples of glass wool (MMVF21 and X607), stone wool, slag wool, and ceramic wool (RCF 1) were intratracheally instilled in female Wistar rats with a single dose of 0.1 to 2 mg in 0.3 ml. Five animals per group were sacrificed after 2 days, 1, 3, and 6 months. Additional sacrifice dates 12 and 18 months after instillation are planned. After low-temperature ashing of the lungs about 200 fibres were analysed in SEM for length and diameter per animal. The number of fibres in the total lung was calculated.

The number of retained fibres in the lung was analysed for different length and diameter fractions. From these data the contribution of the mechanical clearance, breakage of fibres and dissolution of fibres to the overall clearance process was estimated.

First results show that for glass, stone and slag wool samples the breakage of fibres longer than 10 or 20 µm is an important process whereas this was not found for ceramic fibres.

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Source: https://www.industrydocuments.ucsf.edu/docs/hpgl0000

A 60

Investigation on the Biodurability of Chemically Different Stone Wool Fibres

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The biodurability is one of the essential factors for a carcinogenic potential of mineral fibres. The in vivo solubility of commercial fibre products can be influenced by systematic modification of the chemical composition.

Two types of experimental stone wool samples with increased magnesium and decreased aluminia content were compared to a commercial stone wool sample. Sized fractions of these samples with median lengths of 9.3, 7.1 and 6.7 µm, respectively, and median diameters of 1.02, 0.76 and 0.63 µm, respectively, were intratracheally instilled in female Wistar rats with a single dose of 2 mg in 0.3 ml. Five animals per group were sacrificed after 2 days, 1, 3, 6, and 12 months. After low-temperature ashing of the lungs about 200 fibres were analysed in SEM for length and diameter per animal. Number of fibres in the total lung was calculated.

An analysis of fibre number and diameter of different length fractions was used for estimations of three different processes which influence the elimination of fibres from the lung. These processes are: transport by macrophages for short fibres, breakage of fibres and dissolution of fibres. The breakage of fibres with length above 20 µm and the dissolution of fibres was found to be faster in the experimental stone wool samples compared to the commercial sample.

A 61

Quantitative Recovery of Fibers from the Pleural Cavity of the Rat

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The presence of fibers in the pleural cavity is thought to be a necessary component of fiber-induced disease of the pleura. The number of fibers reaching this cavity following exposure by inhalation has yet to be determined with certainty, mainly due to the lack of a reliable method to accomplish this. The present study describes a method designed to quantitate the number of fibers reaching the pleura. Male Fischer-344 rats were anesthetized and given MMVFI0 glass fibers by intrapleural instillation. Thirty minutes later the animals were sacrificed and the pleural cavity was filled with low melting point agarose containing sodium dodecyl sulfate. The agarose was allowed to harden in situ and the resulting cast removed after carefully dissecting away the diaphragm and ribs. The fibers thus entrapped in the agarose cast were recovered by thermal reliquification of the cast followed by centrifugation and were then quantitated by phase microscopy. Histologic examination of the visceral and parietal surfaces of the pleural cavity verified that the detergent/hypotonic action of the agarose selectively lysed only the mesothelial cells, thereby permitting the recovery of cell-associated fibers. The efficiency of recovery for this method was determined following the intrapleural instillation of rats with varying numbers of MMVF10 fibers. Of 1×10^6, 1×10^5, 1×10^4, and 1×10^3 MMVF10 fibers instilled, 72 ± 19%, 88 ± 7%, 94 ± 12%, and 94 ± 14%, respectively, were recovered. These data demonstrate the applicability of this method for the determination of fiber dose to the pleura.

These studies were funded in part by a grant from the Thermal Insulation Manufacturers Association (TIMA).

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A 62

BRDU Incorporation into Rat Lung Cells Following Inhalation of Man-Made Fibres and Asbestos

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Rats were exposed by inhalation to Code 100/475 vitreous microfibre, silicon carbide fibres and a long fibre sample of amosite asbestos. The fibre concentrations were monitored by Phase Contrast Optical Microscopy, using WHO counting rules and adjusted to a target of 1000 fibres/ml. For the studies described here on cell turnover, rats were placed in chambers and exposed for 7 hours only. Following a further 16 hours in room air, the rats received an injection of bromo-deoxyuridine (BRDU); their lungs were removed and fixed one hour later. The presence of BRDU in the nuclei of cells that had divided in the final hour was demonstrated by immuno-staining. The perimeters of terminal bronchioles and their associated alveolar ducts, along with the number of BRDU-positive cells was measured using a computer driven imaging system interfaced to a light microscope. The number of BRDU-positive cells per unit of terminal bronchiole/alveolar duct length was increased in the rats inhaling amosite asbestos, compared to the control (room air-breathing) rats or rats inhaling vitreous fibres.

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2057358141

A 63

Pleural Pathology in Hamsters and Rats Exposed to Instilled Man-Made Vitreous Fibers (MMVF)

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Interspecies differences in mesothelioma incidence have been recently noted in hamsters and rats exposed chronically to inhaled ceramic fibers. The present study was conducted to examine and compare the acute pleural response in the two species when exposed to similar numbers of fibers by intracavity instillation into the pleural space. Groups of hamsters and rats were exposed to either ceramic (RCF-1) or glass (MMVF-10) fibers, dosed on an equal fiber/g body weight basis between the two species. Groups of sham-injected and fiber-injected animals were killed 7 and 28 days post-injection. Visceral and parietal surfaces from predesignated pleural sites were examined by light microscopy including assessment of mesothelial cell proliferation (using immunocytochemical detection of bromodeoxyuridine administered by osmotic minipump). At one week post-injection, similar inflammatory foreign body reactions were found in both rats and hamsters instilled with either the glass or ceramic fiber. At the 28 day timepoint, differences were noted between rats and hamsters in the pattern of reaction on the visceral pleural surfaces. Although both species had marked pleural thickening and fibrosis, generally devoid of the diffuse inflammatory infiltrate noted at the earlier timepoint, hamsters had circumscribed areas of mesothelial cell proliferation. These aggregates of proliferative subsurface cells formed circular structures along the visceral elastic lamina. This unusual pattern of cellular proliferation was noted in both glass and ceramic fiber-exposed hamsters. These results, if confirmed in longer studies, would suggest that the hamster pleural mesothelium reacts in a more proliferative fashion than does the rat.

These studies were funded in part by a grant from the Thermal Insulation Manufacturers Association.

Source: https://www.industrydocuments.ucsf.edu/docs/hpgl0000

Acute Pleural Response of Hamsters and Rats to Inhaled Ceramic Fibers

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We examined the acute pleural response of Syrian golden hamsters and Fischer 344 rats to inhaled ceramic fibers (RCF-1). This man-made vitreous fiber was previously shown to cause a marked difference in mesothelioma incidence in the two rodent species following chronic exposure (rats < 3%; hamsters > 40%). The aim of our experiment was to determine if hamsters and rats differed in their pleural free cell or mesothelial cell response following short-term inhalation of this carcinogenic fiber. We simultaneously exposed rats and hamsters in the same nose-only inhalation towers, 6 hrs/day for 5 days to an aerosol of RCF-1 (900 f/cc) or air. Immediately following five days of exposure, groups of 5 - 6 fiber- or air-exposed rats and hamsters were subjected to pleural (PL) and bronchoalveolar lavage (BAL). Alveolar and pleural free cells were quantified by hemocytometer counts and characterized cytologically on stained cytocentrifuge preparations. One week post-exposure, groups of rats and hamsters were surgically implanted with bromodeoxyuridine (BrdU) containing osmotic minipumps and were sacrificed 72 hours later. Lungs, costal wall, and diaphragmatic tissues were prepared for assessment of histological changes and immunocytochemical determination of mesothelial cell proliferation. Fiber-exposed rats and hamsters showed a marked neutrophil accumulation within the BAL. Fiber-exposed rats had increased pleural free cells, and both rats and hamsters exposed to RCF-1 had mild neutrophil elevations in the PL. BrdU labeling indices were significantly elevated in mesothelial cells lining both fiber-exposed rat and hamster thoracic tissues. Immunostaining of mesothelial cells in both the visceral and parietal pleura was focally distributed. The most prominent cell proliferation was noted in the mesothelial cells lining the thoracic surface of the diaphragm. Significant interspecies differences were not evident with respect to mesothelial proliferation or PL or BAL cytologic alterations. Our results demonstrate that pleural cellular effects occur rapidly in both hamsters and rats following inhalation exposure to ceramic fibers. This finding underscores the need to elucidate the contribution of fiber translocation to resultant pathobiological effects in pleural tissues.

These studies were supported in part by a grant from the Thermal Insulation Manufacturers Association.

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Characteristics of Glass and Amphibole Fibres from the Lungs of Rats Following Inhalation Exposure

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Rats were exposed by inhalation to Code 100/475 vitreous microfibre and a long fibre sample of amosite asbestos. The fibre concentration was monitored by Phase Contrast Optical Microscopy, using WHO counting rules and adjusted to a target of 1000 fibres/ml. Exposure continued for 1 year. At various times during exposure, and during a one year recovery period, rats were killed and fibres recovered from the lungs by hypochlorite digestion. The bivariate size distributions of the fibres present in each examined lung were estimated from SEM measurements of 600 fibres. The mass of fibre in each lung was calculated from the fibre number and size distribution by making assumptions as to fibre shape and specific gravity. The proportional chemical composition of 50 fibres from each point was also measured using EDAX.

The mass clearance of the glass fibre was much faster than that of amosite but the clearance of the glass fibre was slower when expressed in terms of fibre number. In contrast to the amphibole asbestos, the glass fibres had clearly reduced in size either by fragmentation or dissolution. The proportion of silica in the glass fibres was also increased due to leaching of the other elements.

Research funded by the Colt Fibre Research Programme.

Source: https://www.industrydocuments.ucsf.edu/docs/hpgl0000

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Learning from Experiences on Human BAL, which Parameters in Experimental Inhalation Toxicology Can be Used

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In our clinical study in cooperation with the Ruhrlandklinik Essen we are investigating the broncho-alveolar lavage (BAL) from patients with fibrotic lung diseases, especially patients diagnosed as having asbestosis and sarcoidosis.

Cellular changes as well as changes of the lung surfactant and protein content were studied. In comparison to the patients with sarcoidosis, the patients with asbestosis show characteristic alterations of the cellular components, the lung surfactant and the protein content which differentiated both diseases one from the other as well as from healthy volunteers. The dust-exposed patient group was most clearly characterized by the changes in the surfactant. The results from our animal experiments indicate that we have to differentiate between acute dust effects and later changes which become apparent after chronification of the pathological dust effects. In rats, toxic dusts provoke a long lasting granulocytic response in the lung, which cannot be detected in the asbestos-exposed patients. In contrast to this, a good agreement in the reaction of the lung surfactant system was found between humans and animals after chronification of the lung dust response. We conclude that it is basically necessary to apply experiences from clinical studies to experimental testing in animals; in particular, species-specific responses such as the granulocyte influx should be avoided when animal data are evaluated for extrapolating toxicity to human.

2057355143

A 67

Molecular Toxicology Endpoints in Rodent Inhalation Studies

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Although histopathology will continue to be essential for assessing the results of rodent inhalation studies, molecular toxicology endpoints are of increasing importance, as these techniques often complement and extend histopathological examinations.

One of the primary uses of molecular toxicology is determining the delivered dose of the potential toxicant to macromolecules in target tissues. During inhalation studies this is most often done by measuring DNA adducts in the respiratory tract. DNA adducts may be measured specifically (e.g. using monoclonal antibodies or mass spectrometry) or non-specifically (e.g. by using the ^{32}P post-labeling assay). If the inhaled toxicant is found to be genotoxic in the respiratory tract, dosimetry in the systemic circulation may be estimated by measuring hemoglobin adducts.

Another major use of molecular toxicology techniques is the assessment of cellular and molecular changes in target tissues which may precede or be more sensitive than histopathologic alterations. For example, rates of cellular DNA synthesis occurring in target tissues may be quantified at any time during the study by administering the animals either radiolabelled thymidine or the non-radiolabelled thymidine analog bromodeoxyuridine (BrdU).

Pulmonary injury may be assessed in bronchoalveolar lavage fluid using either cellular (e.g. macrophage number, granulocyte number) or biochemical (e.g. alkaline phosphatase, lactate dehydrogenase) techniques. The potential of the inhaled toxicant to produce genetic alterations may be evaluated by examining the chromosomes of pulmonary alveolar macrophages for cytogenetic changes.

In conclusion, quantitative molecular toxicology techniques are expected to assume an increasingly prominent role in the conduct and interpretation of rodent inhalation studies.

Source: https://www.industrydocuments.ucsf.edu/docs/hpgl0000

Questions About the Risk Assessment Methods Using Linear Downward Extrapolation

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A recent report by the Health Effects Institute - Asbestos Research (HEI-AR) calculates the risk of involuntary exposure to very low levels of environmental asbestos fiber (EAF) by linear downward extrapolation from the mortality of workers exposed for 20 years. However, this type of extrapolation rests on a number of major assumptions which needs careful scrutiny. First, is the relative lung cancer risk of asbestos exposure linearly progressive? This is difficult to determine because most human exposures have been to high doses. However, animal data appears to conflict with that hypothesis. Second, is it true that the composition od EAF is equivalent to asbestos inhaled in mining or fabricating? Third, is there evidence to suggest that the health effect of EAF exposures of children, seniors, patients, institutionalized handicapped and the chronically ill are the same as those of healthy workers? Evidence of asbestos-related disease among family members of workers demonstrate that the risk observed for involuntary exposure to EAF is substantially larger that can be estimated from downward extrapolation and suggests additional approaches to risk evaluation. The problems raised by the HEI-AR Report are important because their resolution may affect methods of risk assessment to low dose exposures such as to EAF, to particulates, to radioactive particles and to secondary exposure to tobacco smoke.

2057358144

Use of Asbestos, Health Risks and Induced Occupational Diseases in the Former East Germany

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In the period from 1960 to 1990 about 1.4 million tons of asbestos were imported and mainly processed into asbestos-cement products for the building industry. The production was concentrated in the former counties of Magdeburg and Dresden. In the large-scale chemical industry, asbestos was primarily used as insulation and fire prevention material, etc. The asbestos was imported from the former Soviet Union, smaller amounts came from Canada (chrysotile asbestos, confirmed by material investigations, too). The import of crocidolite was stopped in the 1960s. The use of asbestos for sprayed-on insulations has been prohibited since 1969. Health care measures for users of asbestos were prescribed by law.

Morbidity and mortality developments caused by exposure to asbestos were carefully monitored by occupational physicists. The autopsy rate which was relatively high in the former East Germany contributed considerably to seeing the effect of asbestos on the development of bronchial carcinoma and mesothelioma much more objectively from an epidemiological point of view. While the frequency of silicoses, for example, continuously decreased, an increase in occupational malignant tumours, caused in 90 % of the cases by asbestos, has been obvious since the 1970s.

In the German Federal State of Saxony-Anhalt, approximately 600 asbestoses, almost 2,700 pleural changes caused by asbestos, 617 asbestos-induced mesotheliomas and 787 bronchial and laryngeal carcinomas were recorded in the period from 1960 to 1990. Principles and measures of diagnosis and evaluation were in compliance with pertinent international standards. A considerable percentage of the mesotheliomas are solely due to exposure to chrysotile asbestos. Detailed investigations describe and quantify this relationship. In our opinion, the easy-to-survey asbestos imports, the results of material studies and the diseases found confirm the carcinogenic potency of chrysotile asbestos beyond all doubt.

Source: https://www.industrydocuments.ucsf.edu/docs/hpgl0000

Separation, Deposition and Lung Clearance of Fibrous Solid Particles (Review)

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The geometry as well as the aerodynamic behavior of highly dispersed mineral fibers are determined for their separation and deposition mechanisms in filter systems, including animal and human airways. Furthermore, the mechanical and chemical lung clearance of deposited fibrous particles depends strongly on their geometry, size and biochemical persistency.

The review is dealing partly with own experimental results, partly with newest publications, which have described the mechanics of fiber separation and deposition in animal and human airways using theoretical models and animal experiments.

In several animal experiments the clearance kinetics of deposited asbestos and other mineral fibers was investigated, too. The review is evaluating all the results and discussing the future development and research needs.

2057358145

Long Term Dust Exposure in Foundry Workers May Lead to Impaired Lung Function

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In short term or cross sectional studies dust exposure is often found to result in symptoms like cough and phlegm, but not functional impairment of the lungs. Extensive occupational surveillance studies on the other hand revealed doubling of prevalence rates of chronic obstructive lung disease in workers (smokers as well as non-smokers) exposed to dust above 10 mg/m^3 total dust for more than five years.

To look for dose-effect-relationships between low long term dust exposure and lung function we did a 15-year longitudinal study in foundry workers. Dust exposure has been monitored by stationary and if necessary personal sampling, 2-step gravimetric measurement and calculation of mean annual doses for each subject. The cohort comprising 273 subjects at the start was controlled by standardized questionnaire, clinical status, spirometry, flow-volume-curve, oscilloresistometry and chest X-rays.

Whereas mean annual dose of the last year expectedly did not lead to dose-effect-relationships in regard of lung function, mean concentration of both, total or respirable dust, for 15 years of exposure did. Decline of FVC differed between 26 and 116 ml/year dependent on mean concentrations of dust. Based on decomposition analysis of mixed distribution of lung function data estimated thresholds revealed between 3,95 and 5,91 mg/m^3 for total and 1,02 and 2,34 mg/m^3 for respirable dust.

In line with British studies on large cohorts of coal workers these results indicate the need for lower limit values to prevent each functional respiratory impairment by occupational dust exposure.

Source: https://www.industrydocuments.ucsf.edu/docs/hpgl0000

Characterization of Historical Samples of Nickel Refinery Dusts from the Clydach Refinery

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In characterizing nickel refinery dusts, we have applied inductively coupled plasma emission spectroscopic quantitative analysis and X-ray powder diffraction studies and have developed single particle techniques using quantitative image analysis, SEM-EDAX, and finally laser beam ionization mass spectrometry analysis (LIMA) for surface analysis. We have applied these methods to historical samples from the nickel refining plant at Clydach in Wales. There were 2 historical samples believed to be processed material and raw input (Bessemer matte) from 1920 and 1929. The former material is microcrystalline, aggregated into particles with a mean diameter of 3 µm. The 1920 sample comes from the period when initiation of respiratory cancers at Clydach was at its highest whereas by 1929 the initiation had dropped almost to background levels. The most significant difference in elemental composition is the presence of 10 % arsenic in the 1920 sample as compared with 1 % in the 1929 sample. Of particular interest is the presence of a component, in the 1920 sample only, identified as the mineral orcelite,a copper-iron-nickel-arsenide-sulphide mineral, $(Ni,Fe,Cu)_{4.2}(As,S)_2$.

2057358146

Development and Characterization of Rat Lung Epithelial Cell Lines for Toxicity Studies

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Recent studies suggest that alveolar type II cells may be key effectors of the lung's response to inhaled particles. Cell cultures capable of extended multiplication and subculture are important for detailed *in vitro* studies on the role of type II cells in pulmonary toxicity and carcinogenesis. In order to establish such a target cell system, we developed methodology to isolate and culture type II cells under conditions which preserved their proliferative capacity and applied lipofection to introduce an immortalizing gene into the cells. Briefly, alveolar type II cells were isolated from male F344 rats using airway perfusion with a pronase solution followed by incubation for 30 minutes at 37°C. Cells obtained by pronase digestion were predominantly epithelial in morphology and were positive for Papanicolaou and alkaline phosphatase staining. These cells could be maintained on an extracellular matrix of fibronectin and type IV collagen in a low serum, insulin-supplemented Ham's F12 growth media for 4 - 5 passages. Primary cultures of rat alveolar epithelial cells obtained by this method were transformed with the SV40-T antigen gene. Using this approach two immortalized cell lines were obtained; one cell line (line RLE-6T) exhibits positive nuclear staining for the SV40-T antigen and the other does not (line RLE-6TN). The properties of the lines were studied in detail. After >50 population doublings, the RLE-6T cells stained positive for cytokeratins 8, 18 and 19 and alkaline phosphatase and possessed lamellar inclusion bodies (phosphine 3R staining, electron microscopy) indicating that the line exhibited characteristics of alveolar type II cells. The RLE-6TN cells exhibited similar characteristics but did not show positive alkaline phosphatase staining. Preliminary studies indicate that the RLE-6T cells can express proteins important to particle-induced inflammatory cell recruitment and activation. These cell lines represent potentially useful tools to study the role of pulmonary epithelial cells in neoplastic and nonneoplastic lung disease.

Source: https://www.industrydocuments.ucsf.edu/docs/hpgl0000

Significance of Length and Diameter of a Durable Fibre on its Carcinogenic Potency

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It has been generally accepted that size and shape can determine the carcinogenicity of an elongated particle. However, exact quantitative relationships between length and diameter of durable fibres and their carcinogenic potency are still unknown. While it is highly probable that a long fibre is more carcinogenic than a short one, the establishing of a relationship between fibre diameter and carcinogenic potency is complicated by the extreme difficulty to apply dust masses containing sufficient numbers of fibres with diameters > 2 µm in any test model. We analysed the data from inhalation and implantation studies by statistical regression techniques. The results do not confirm an interpretation of these studies that the carcinogenicity of fibres with lengths below 5 µm or diameters above 1 µm is virtually negligible. For example, the results of the inhalation study of Davis and Jones (1988) with "long" and "short" chrysotile fibres as well as of the intrapleural implantation studies of Stanton et al. (1981) can be plausibly explained under the assumption of a continuous distribution of the carcinogenic potency dependent upon length and diameter over a large range. Furthermore, recent inhalation studies (Mast et al., 1992) have shown a relatively high tumour incidence with rather thick refractory ceramic fibres as compared to much higher fibre numbers of chrysotile asbestos.

2057358147

Biokinetics of Thorium and Daughter Radionuclides after Deposition in the Rat Lung as Fluoride and Hydroxide

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The dosimetric model of the respiratory tract developed by the International Commission on Radiological Protection (ICRP) assumes the 'metabolic behaviour of all the radioactive progeny is the same as that of the ancestral radionuclide'. If this was the case, measurements of the daughter radionuclides ^{212}Pb, ^{212}Bi or ^{208}Tl in the chest, or thoron (^{220}Rn) in breath would enable reliable assessments of ^{232}Th or ^{228}Th activity in the lungs. However, there is a lack of data which either supports or contradicts this assumption.

The aims of the work summarised here were to investigate the lung retention kinetics of Th and daughter radionuclides after their intratracheal instillation as fluoride or hydroxide. The amounts of Th administered ranged from 18 pg (^{228}Th) to 6.5 µg ($^{228+232}$Th) in order to reflect occupational exposure under different conditions.

The ratios of ^{228}Th to ^{212}Pb, initially 1:1, which were present in the lungs at 1d, 7d and 28 d after exposure are given in the Table; the ratios of ^{228}Th to ^{212}Bi and ^{208}Tl under the same conditions were similar. The variability of the ratios can be attributed to both the lung retention kinetics for the different chemical forms of the radionuclides and the mass of Th administered.

Ratio of ^{228}Th to ^{212}Pb retained in the rat lung, mean ± SE, N = 5

	Th fluoride		Th hydroxide	
days after exposure	low mass	high mass	low mass	high mass
1 d	11 ± 1.3	3.9 ± 0.3	21 ± 3.9	13 ± 1.3
7 d	28 ± 0.1	4.4 ± 0.3	182 ± 29	110 ± 19
28 d	91 ± 23	4.8 ± 1.1	155 ± 17	64 ± 11

The results demonstrate that after deposition in the lungs the transportability of the daughter radionuclides is substantially greater than the parent. This casts doubt on the widespread application of *in vivo* techniques for assessing intakes. Work is in progress to investigate the lung retention kinetics of Th and daughter radionuclides after administration as nitrate.

Source: https://www.industrydocuments.ucsf.edu/docs/hpgl0000

Modeling Particle Deposition in a Bifurcating Airway

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Experiments on deposition of particles in the lung have demonstrated the existence of regions of high deposition or "hot spots" near conducting airway bifurcations. Disease may originate in these regions. Analytical studies of particle deposition have neglected the complex secondary flows at the bifurcation. Although enhanced deposition at bifurcations is due to increased impaction and interception, secondary flows may also increase both sedimentation and diffusion losses. Therefore, improved models of particle deposition should include secondary flow effects. In this study, steady airflow and particle transport and deposition are calculated for a three-dimensional model of a bifurcating airway. The model domain was based on human data and, for simplicity, was defined so that all cross sections parallel to the plane of the bifurcation were identical. Steady flow within this domain was solved numerically by a finite element method using the commercial software package FIDAP (Fluid Dynamics International, Evanston, IL, USA). Flow fields were first computed for Reynolds numbers up to 1000, which include flow in the second generation of the human lung. Using these calculated flow profiles, an individual particle trajectory within the air stream was simulated by numerically solving the fundamental differential equations of particle motion. The simulation included the effects of impaction, diffusion, and sedimentation. Deposition efficiencies and patterns were obtained by simulating a large number of particles. In addition, for ultrafine particles for which diffusion is the sole mechanism of deposition, the convective-diffusion equation for particle distribution was solved using FIDAP and particle loss to the airway walls was determined. Results of both analyses show clear sites of enhanced deposition in the daughter airway near the carina. The locations of these sites appear to change with flow Reynolds number and particle size. The results also show higher deposition than previous analytic models, demonstrating the significance of secondary flow effects.

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A Strategy for Combining Experimental, Large-Scale, and Site-Specific Models to Determine Fiber Deposition in Animals and Man

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In order to characterize potential human risks from exposure to fibers, an understanding is needed of the deposition and retention of fibers at various sites within the respiratory tract. A critical first step involves predicting the deposition of fibers relative to interspecies differences in respiratory tract structure and breathing patterns. A combination of models of varying complexity is needed to model deposition with resolution from a macro- to microscopic scale for the upper respiratory tract (URT), the tracheobronchial (TB) airways, and the gas-exchange regions of the lung. We are developing a strategy for combining experimental, large-scale, and site-specific models to determine fiber deposition in animals and man. Modeling efforts can be categorized into three broad areas: URT whole lung and site-specific modeling. Given the lack of experimental data on the deposition of fibers in the nose, near term URT dosimetry efforts will focus on experimental studies to determine deposition efficiencies in the head for fibers of varying length and diameter following nose-only inhalation exposure. Longer term, we will use information from flow field simulations obtained by numerically solving the three dimensional Navier-Stokes equations in wire-frame style grid models. Such models have been developed for a rat from serial step section reconstructions. MRI or CAT scan images will be used for a human URT grid. For whole lung modeling, we have developed a mathematical model of deposition in individual airways and acini in a multiple-path lung structure. Integral to this effort is the Lovelace database, which contains measurements of conducting airway length, diameter, and branching angles for casts of the lungs of various species, including rats and humans. The structural model for the alveolar region will be based upon data on the size and branching structure of individual pulmonary acini available from investigators at the Duke Center for Extrapolation Modeling. The variation in acinar deposition can be estimated by attaching acinar units of different sizes from the data set to terminal bronchioles and then calculating the resulting deposition. The site-specific portion of the modeling effort has the following two components: a solution of the Navier-Stokes equations and Monte Carlo simulations of fiber transport and deposition. The Monte Carlo procedure will track both the fiber location and orientation. These models are being used to evaluate deposition efficiencies in conducting airway bifurcations and alveolar ducts. The efficiencies will be used to refine the whole lung model.By linking the types of models described above for the three major respiratory tract compartments, deposition of fibers from the nares to the most distal alveolar sacs can be predicted. When combined with experimental studies that enable estimation of the bimodal, bivariate, lognormal distribution of particle and fiber lengths and diameters, this modeling strategy will provide a powerful tool for conducting more accurate human health risk assessments.

Source: https://www.industrydocuments.ucsf.edu/docs/hpgl0000

Bimodal Bivariate Lognormal Distributions in the Application of Inhalation Toxicology Specific to the Measurement of Fiber and Particle Dosimetry

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A complete description of the inhaled particle and fiber size distribution is required in order to allow current, past, and future "index" populations to be correlated with biological responses. In most studies the inhalation of fibers is accompanied with the inhalation of particles of the same material. A population of fibers and particles can be described by a bimodal, bivariate lognormal distribution. The distribution consist of a bivariate lognormal distribution of fibers, a bivariate lognormal distribution of the accompanying particles, and the percentage of particles. The five parameters of each bivariate lognormal distribution consists of the median length, the median diameter, the geometric standard deviation for length, the geometric standard deviation for diameter, and the correlation between the log of the length and the log of the diameter. Both a hand method and a semi-automatic method were developed for measuring the eleven parameters necessary to describe the bimodal, bivariate lognormal distribution in samples of a refractory ceramic fiber, RCF, and a glass fiber. For example in a sample of RCF the measured fiber distribution was 13.0 µm, 0.97 µm, 2.3, 1.9, and 0.47 respectively with 41 % particles of distribution 2.8 µm, 1.91 µm, 1.8, 1.7, and 0.78 respectively. Similar measurements on a glass fiber sample produced a fiber distribution described by 19.7 µm, 1.4 µm, 2.4, 1.7, and 0.42 respectively with 10 % particles of distribution of 1.3 µm, 0.98 µm, 2.2, 1.9, and 0.98 respectively. Given the equation for the complex surface we then calculated the fraction of the total number of particles contained within specific length and diameter boundaries. More than 0.3 count % of the total RCF sample (0.1 % of the total glass fiber/particle sample) met Stanton's definition of an index fiber ($d \leq 0.25$ µm, $l \geq 8.0$ µm). The distributions measured could also be split out to estimate the index fibers defined by Lippmann and Timbrell for mesothelioma, carcinoma and fibrosis. For example, approximately 0.003 count % of the total RCF sample (< 0.001 % of the total glass fiber/particle sample) fit the definition of index fibers for mesothelioma ($d \leq 0.1$ µm. $l \geq 5.0$ µm).

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2057358149

Mathematical Model of Deposition, Retention and Clearance of Insoluble Particulates in the Alveolar Lung

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The model to be described is designed as a simulation of actual processes, as identified in numerous studies rather than derived from the modelling of data. It will describe the process of deposition of particulates in the alveolar region, and their subsequent retention and clearance, in terms of the mechanisms of cell biology , specifically that of phagocytosis by alveolar macrophages (AM) and neutrophils (PMN). The fate of free particulates deposited in the alveolar region may be summarised and consequently modelled as follows: (a) Particulates may be cleared from the alveolar surface to the tracheobronchial region as free particulates or within AMs and PMNs. (b) Free particulates in the alveolar region may cross the epithelium into the interstitium. Once in the interstitium as free particulates they may be (c) cleared to the efferent lymph nodes, (d) phagocytosed by interstitial macrophages (IM) or, eventually, (e) accumulate in the subpleural basement membrane. Phagocytosed particulates may either be sequestrated in the interstitium or eventually removed to the lymph nodes.

In particular, the model will represent local sequestration as two, morphologically different compartments rather than one. The alveolar sequestration compartment is the consequence of the loss of macrophage mobility when excessive amounts of particulates are phagocytosed. This is most pronounced when, at very high lung burden, the clearance of particulates from the lung becomes impaired to the extent that the particulate at post-exposure decreases with increasing lung burden. This is known as the overload phenomenon. On the other hand, the interstitial sequestration compartment is composed of particulate-laden IMs which, if fibrosis develops, can become trapped by the proliferation of fibroblast cells activated by the cytokines released during phagocytosis.

Source: https://www.industrydocuments.ucsf.edu/docs/hpgl0000

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Human Exposure to Insoluble Isometric Particles

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While toxicology assessments and long term inhalation studies generally aim to evaluate the health effects of exposure to a single compound or mixture, humans frequently have no choice but to inhale complex mixtures, ranging from gases to solid particles. Environmental exposures of the population often involve low level exposures to complex mixtures whereby gases, liquids and low molecular weight solid particles are adsorbed on the solid surfaces. Occupational exposures to insoluble particles generally involve higher exposures to one or few materials or mixtures. With the changing nature of work, several of the occupational exposures such as in mining are being shifted from the developed to the less developed countries, often resulting in less rigorous exposure control measures. Exposure measurement is frequently the weakest link of the risk assessment process. The presentation will review the scope of environmental and occupational exposure to insoluble isometric particles.

Introduction

Fine Particle Measurement Techniques

Environmental Exposure

Occupational Exposure

20573581150

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Particle Deposition and Accumulation in Human Lungs

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Particle accumulation in human lungs is highly dependent upon deposition site for both: 1) local retention at or near the initial site; and 2) as a determinant of the pathways for clearance from the lungs and translocation to other thoracic retention sites. Earlier research and models emphasized deposition and accumulation within large anatomic regions that differed markedly in structure and retention times, i.e., upper respiratory tract (head airways); lung conductive airways (tracheobronchial tree); and gas exchange region (pulmonary or alveolar region). However, it is now clear that such gross subdivisions are inadequate for realistic toxicant dosimetry and for understanding the pathogenesis of chronic lung diseases. Within each of the major anatomic regions, there are marked variations in both the surface density of particle deposition and clearance rates. This paper reviews current knowledge of the influence of factors affecting particle deposition patterns and clearance rates. These factors include: 1) the properties of the particles (aerodynamic size, particle shape and composition); 2) the airway geometry (airway length, cross section, extent of taper, branching angles); 3) nature and extent of pre-existing lung burdens and diseases, etc.; 4) ventilation parameters (velocity, tidal volume, frequency, times of breath holding, turbulence, and oral vs. nasal inhalation); and 5) other factors (such as axial-core flow of inhaled particles induced by the beating heart). It also reviews current knowledge of the transmembrane transport of deposited particles into interstitial sites and along translocation pathways to more remote sites of accumulation and toxic effects.

Source: https://www.industrydocuments.ucsf.edu/docs/hpgl0000

Mineral Analysis of Human Autopsy Lungs - Comparisons with Predictive Data

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In the past 15 years a considerable body of data has accumulated on the particle burden of human autopsy lungs. In the general population, both the airway mucosa and the parenchyma carry very substantial burdens (hundreds of millions of particles/gm dry tissue) of inhaled ambient particles. In nonsmokers, particle concentration in the airways increases with decreasing airway diameter and increasing distance from the carina, in accord with theoretic models of deposition. Carinas appear to be sites of preferential particle accumulation, but our initial data suggest that the ratio of carinal to tubular airway concentration is very variable. Many, but not all, smokers do not show the expected pattern of particle deposition, implying that some but not all individuals have particular sensitivity to cigarette smoke. Calcium carbonate particles in the airways appear to be useful as a direct smoke tracer. The distribution of such particles corresponds to mathematical models of smoke deposition, with the highest concentrations found in the largest airways and in the parenchyma.

Asbestos fibers are found in the lungs of the general population and in those with occupational exposure. Distinct, reproducible, patterns of fiber concentration and disease are observed and these are different for chrysotile asbestos, for which both mesothelioma and asbestosis appear at very high lung burdens, and amosite or crocidolite asbestos, for which mesothelioma appears at much lower burdens than does asbestosis. Contrary to prediction, there is no clear evidence that either mesothelioma or asbestosis are preferentially associated with long high aspect ratio fibers in man. Fiber surface area also shows no correlation with disease. However, pleural plaques are associated with high aspect ratio fibers for all types of asbestos exposure. More work is needed to determine what mineralogic factors relate to the appearance of specific diseases in exposed workers.

20573581S1

Epidemiology After Chronic Dust Exposure

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It is well known that chronic dust exposure results in various types of lung diseases, like pneumoconiosis, silicosis or chronic bronchitis. However, the dose-response relation is different for several dust compounds, e.g. for cement dust the risk for chronic bronchitic reactions is the steepest one. Several reasons will be discussed.

In recent years the research is focussed on the question of the carcinogenic effect of several dust compounds. The special interest is on silica dust, cement dust and carbon black.

I want to present some findings especially in relation to silica and cement dust.

For silica dust numerous results of epidemiological studies are published. Some studies are showing an association between the occupational exposure and lung cancer whereas others are failing. In most studies, the information about the major confounding factor, smoking, is sparse. The increased risk is concentrated to some types of industries. In coal mines no association can be found.
Some possible reasons in the literature will be discussed.

In cement dust very recently some studies have reported an association to cancer.
These findings together with other studies will be discussed.

Source: https://www.industrydocuments.ucsf.edu/docs/hpgl0000

Sub-Chronic Inhalation Study in Rats, Using Aged and Diluted Sidestream Smoke from a Reference Cigarette

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Male Sprague-Dawley rats were exposed six hours per day, 5 days per week for up to 13 weeks to aged and diluted sidestream smoke (ADSS), used as a surrogate for Environmental Tobacco Smoke (ETS), at concentrations of 0.1 ("typical"), 1 ("extreme") or 10 ("exaggerated") milligrams (mg) of particulates per cubic meter. Sub-groups of animals were killed after 1 and 4 weeks of exposure. Animals were exposed nose-only, inside whole-body chambers, to ADSS from the 1R4F reference cigarette.

End-points included histopathology, CO-oximetry, plasma nicotine and cotinine, clinical pathology, and organ and body weights.

The target particulate concentrations were achieved; at the exaggerated exposure they resulted in carbon monoxide (CO) concentrations in excess of 50 ppm. Particle size distributions showed that the aerosols were completely respirable: the mass median diameter values were less than 1 µm. The only pathological response observed was slight to mild epithelial hyperplasia in the rostral nasal cavity, in the exaggerated exposure group only. No effects were noted at extreme or typical exposures. The changes were similar in animals killed after 4, 28 or 90 days, and were also similar to those noted in an earlier experiment with only 14 days duration, indicating that the change does not progress with increased exposure duration from 4 to 90 days. The nasal change was absent in a sub-group of animals kept without further treatment for an additional 90 days, indicating complete reversibility.

Overall, the end-points used in the study demonstrated that (i) there was no detectable biological activity of ADSS at typical or even 10-fold ETS concentrations, and (ii) that the activity was only minimal at very exaggerated concentrations, in one region of one organ only.

In conclusion, the study showed only minimal effects in animals exposed to massive exaggerations of real-world concentrations of ETS. The NOEL for the study, based on the nasal pathology, was > 1 mg/m^3.

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Comparative Inhalation Studies in Rodents, Using Smoke from Cigarettes that Heat Rather than Burn Tobacco, with Special Reference to Particulates

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Sprague-Dawley rats were exposed nose-only for 1 h/day on weekdays for 13 weeks to the smoke from test and reference cigarettes, at low, medium and high concentrations (200, 400 and 800 mg of particulates per cubic meter). In the test cigarette the tobacco was heated rather than burned; the tobacco-burning University of Kentucky 1R4F cigarette was used as a reference.

End-points included histopathology, CO-oximetry, plasma nicotine and cotinine, clinical pathology, and organ and body weights.

Blood carboxyhemoglobin concentrations approached those associated with lethal concentrations of CO; the smoke from the reference cigarette resulted in substantial reductions in breathing frequency whereas the smoke from the test cigarette did not. The availability of nicotine from both cigarette types was very similar; plasma nicotine concentrations approached 300 ng/ml in the high exposure groups.

Animals in both high exposure groups showed increased heart weights when compared with shams. Earlier work has shown that this cardiomegaly is probably caused by the very significant elevations in blood carboxyhemoglobin concentrations.

The histopathology indicated that most of the changes observed in the reference animals were absent in the test animals. When changes were seen in the test groups (primarily in the larynx) they were substantially reduced when compared with the reference groups and were completely reversible. There were no novel changes in the test animals.

Overall, the study showed a substantial reduction in the biological activity of the smoke from the test cigarette when compared with the smoke from the reference cigarette. The importance of the nature of the particles in inhalation toxicology studies will be described.

Source: https://www.industrydocuments.ucsf.edu/docs/hpgl0000

Effects of Cigarette Smoke Exposure on Rat Lung Clearance of Insoluble Particles

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In addition to inducing toxic effects, cigarette smoking can retard the clearance of inhaled, relatively insoluble particles in both humans and experimental animals. While examining the effects in rats of combined exposure to cigarette smoke and radiation on cancer, we also studied the clearance of inhaled radiolabeled fused aluminosilicate particles (^{85}Sr-FAP) in rats chronically exposed to cigarette smoke. Beginning at 6 weeks of age, groups of 24 CDF® (F344)/CrlBR male and female rats were chronically exposed in whole-body exposure chambers to either filtered air or to mainstream cigarette smoke given at concentrations of 100 or 250 mg/m^3 total particulate matter for 6 hours/day, 5 days/week. Animals received the ^{85}Sr-FAP tracer particles by single, nose-only acute inhalation exposure after 14 weeks of smoke exposure. Retention of the ^{85}Sr over 6 months was measured by periodic whole-body counting and was modeled using two-component, negative exponential functions. An analysis of variance demonstrated a highly significant ($p < 0.001$) influence of smoke exposure concentration on clearance, with increasingly retarded particle clearance with increasing smoke exposure concentration. Less clearcut were differences between males and females, although at the highest smoke concentration, males cleared significantly ($p < 0.05$) more of the ^{85}Sr than females. Thus, our results indicate that chronic smoke exposure significantly retards particle clearance from the lungs of rats. Moreover, because this effect is similar to that observed in humans, these results suggest that the rat constitutes a useful model for examining the relationships between cigarette smoking and disposition of inhaled particles. (Research supported by Assistant Secretary for Defense Programs, U.S. Department of Energy under Contract No. DE-AC04-76EV01013.)

2057358153

Uptake of Respirable Suspended Particles (RSP) by Exposure to Environmental Tobacco Smoke (ETS)

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Biomarkers such as carboxyhaemoglobin (COHb), nicotine, cotinine and thiocyanate in body fluids, which are most frequently used for the quantification of tobacco smoke exposure indicate the uptake of gas phase ETS constituents by non-smokers. However, according to in vitro experiments and in vivo animal studies, the constituents of ETS, which may be of most relevance for chronic adverse health effects are mainly located in the particulate phase. Biomarkers specific for the exposure to ETS particles are currently not available. As a result, particle uptake can only be estimated on the basis of ETS particle concentrations in ambient air and respiratory tract deposition rates. Different experimental and theoretical approaches revealed that the deposition rate of ETS particles is in the range of 10 - 15 %, which is significantly lower than that for active smoking (50 - 90 %). The contribution of tobacco smoking to indoor air particle levels can be estimated by measuring solanesol as a tobacco-specific, ETS particle-bound marker. On the basis of our own investigations in an experimental room and in real-life environments as well as of data from the literature, we calculated that the daily uptake dose of RSP of an average non-smoker exposed to ETS amounts to 10 - 30 µg, which is 0.006 - 0.018 % of the daily particle dose of an average smoker (20 cigarettes/d). This very low uptake dose of tobacco smoke particles is at variance with epidemiological studies, which report that the risk for lung cancer in ETS exposed non-smokers amounts to up to 20 % of the smoking-related lung cancer risk. Reasons for this discrepancy are discussed.

Source: https://www.industrydocuments.ucsf.edu/docs/hpgl0000

Possible Effects on Occupational Lung Cancer from Smoking-Related Changes in the Mucus Content of the Lung

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There appears to be consistent findings that relative lung cancer risks for occupationally exposed smokers compared to unexposed smokers are consistently smaller than relative lung cancer risks of occupationally exposed nonsmokers compared to unexposed nonsmokers. Also smokers in dusty occupations report less irritation than nonsmokers. These observations have been called by some a "Healthy Smoker Effect". Moreover beagle dogs exposed to uranium ore dust and tobacco smoke develop significantly fewer respiratory cancers than dogs exposed only to uranium dust. One reason for these changes may be the thickened mucus layer in tracheobronchial regions of smokers. Physiological changes in the lung due to smoking may decrease the effects of radioactive or toxic particles in the bronchial region by promoting faster clearance in that region and reduce penetration to the sensitive basal epithelial cells. Particle clearance from the alveolar region may not affect differences in cancer response between smokers and nonsmokers because of slow migration. If mucus formation reduces somewhat the risk of lung disease of workers, preventive measures may exist to protect certain occupations from dust hazards by increasing mucus production in the lung.

2057358154

Histopathological Findings in the Rat Respiratory Tract in a 90-d Inhalation Study Using Sidestream Smoke of the Standard Reference Cigarette 2R1

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The histopathological findings observed in the nasal and laryngeal epithelia of male Sprague Dawley rats nose-only exposed 7h/d, 7 d/w, for 90 days to sidestream smoke at TPM concentrations of 2 µg/l and 6 µg/l (designated as low and high dose groups, respectively) are described herein.

In the larynx, slight hyperplasia of the squamous epithelium at the base of the epiglottis (1 of 9 rats) and at the lower surface of the vocal cords (1 of 10 rats) was seen in the low dose group. At the same sites, the same finding was also observed in the high dose group (2 of 8 rats and 10 of 10 rats, respectively). Also in the latter group, slight hyperplasia of the cuboidal epithelium at the ventral depression (4 of 10 rats) and of the squamous epithelium at the vocal folds (3 of 10 rats) as well as slight squamous metaplasia of the pseudostratified cuboidal epithelium at the floor of the larynx (4 of 10 rats) and at the upper medial surface of the vocal cords (9 of 10 rats) were seen. The morphometrical determination of the laryngeal epithelial thickness at the arytenoid projections revealed a concentration-dependent increased thickness at the floor of the larynx and the lower medial surface of the vocal cords that was statistically significant only in the high dose group. All the aforementioned findings in the larynx following sidestream smoke exposure have not been described in literature. In the rostral nasal cavity, slight and/or slight/moderate reserve-cell hyperplasia was seen in both dose groups (1 of 10 rats in the low dose group and 10 of 10 rats in the high dose group). No sidestream smoke-related findings were observed in trachea and lungs. All sidestream smoke-related findings reversed completely or in part during the 21-d recovery period.

These findings indicate that sidestream smoke in concentrations far above the levels reached in occupied spaces with smoking induces reversible adaptive changes in the epithelium of the upper respiratory tract of the rat.

Source: https://www.industrydocuments.ucsf.edu/docs/hpgl0000

Influence of Aging and Surface Contact on the Composition of Cigarette Sidestream Smoke - Models for Environmental Tobacco Smoke

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Environmental tobacco smoke (ETS) is a complex mixture derived from sidestream smoke of burning cigarettes and mainstream smoke exhaled by smokers. Its composition is highly variable in indoor environments as it undergoes chemical/physical changes due to dilution and aging influenced by contact with materials. Since it is practically impossible to reproducibly generate "real" ETS, only models of ETS can be used for analytical and biological testing. To obtain such ETS models, diluted sidestream smoke was room-aged under various conditions.

In a series of experiments performed in an empty 30 m^3 experimental room (conditioned air, epoxy-coated walls, PVC-flooring), the concentrations of total particulate matter (TPM), carbon monoxide, nicotine, aldehydes, ammonia, and hydrogen cyanide were determined in continuously generated diluted fresh and room-aged sidestream smoke. The TPM concentration of the fresh sidestream smoke was 11 µg/l. At a smoke age of 1.5 h, nicotine and TPM were reduced to approx. 30 and 70 % of their respective fresh sidestream smoke concentrations, whereas the concentrations of the other components determined were not affected. When materials such as wallpaper or wool or wood were present in the room, the nicotine concentration was most strongly affected. Nicotine reductions to approx. 30 to 16 % of that of the fresh sidestream smoke as well as pronounced reductions for TPM, ammonia, formaldehyde, and hydrogen cyanide were seen. No differences were seen for carbon monoxide, acrolein, acetaldehyde, and propionaldehyde.

Over a 90-day period, fresh sidestream smoke was continuously generated 6 h/day. In parallel, room-aged sidestream smoke with a mean age of 1.5 h was continuously generated by passing fresh sidestream smoke through a 30 m^3 room equipped with a fixed set of materials. Over the 90-day period both kinds of smoke could be reproducibly generated, no trends for the concentrations being seen. The TPM concentrations of the fresh and room-aged sidestream smoke were 8.7 ± 0.7 µg/l and 2.6 ± 0.3 µg/l, respectively. The respective nicotine concentrations were 2.2 ± 0.4 µg/l and 0.5 ± 0.1 µg/l. With the setup used, significantly different ETS models were reproducibly generated.

Extrapolation of Results from Animal Inhalation Studies to Humans?

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An important component of the risk assessment process involves the qualitative and quantitative extrapolation of results from animal inhalation studies to humans. One goal of such extrapolation is to quantify a human risk from inhaled particulate matter. This quantitation is necessary to assess the potency of an inhaled particulate compound which may cause an adverse effect. With respect to lung "particle overload" effects one can predict from results of rat studies that an impaired lung clearance function may occur in humans occupationally exposed to particle concentrations of ~1 mg/m^3, a concentration considerably below present TLVs for "nuisance" particles. However, the question can be raised: Is the rat the appropriate model to use for both qualitative and quantitative risk extrapolation? This question is prompted by results showing significant species differences in long-term particle overload studies: On the one hand, long-term effects in such studies in rats resulted in pulmonary fibrotic and even tumorigenic changes, yet, on the other hand, mice did not develop such adverse effects during chronic particle exposure. In order to address the question about the appropriate species for extrapolation to humans a better understanding of basic mechanisms leading to the adverse effects is required, and the observed species differences between rats and mice should be exploited to obtain such understanding. One approach is to analyze differences in pulmonary cellular, biochemical and molecular-biological responses to particles *in vivo* between rats and mice and to compare these to responses from *in vitro* exposures between rat, mouse and human lung cells/tissue. Respiratory tract dosimetry including molecular dosimetry should be one important aspect of these studies. Complementary studies can be performed with archival fixed tissues of past long-term rat and mouse inhalation studies using modern molecular-biological techniques to assess cell proliferative responses and expression of cytokines and proteins. Together, these *in vivo/in vitro* studies will allow conclusions to be drawn from analogy to strengthen the development of mechanistically-oriented extrapolation of results from one or the other species to humans, and thereby improve human risk assessment.

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Contribution of Inhalation Bioassays to the Assessment of Human Health Risks from Solid Airborne Particles

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The usefulness of rodent inhalation bioassays for estimating health risks from human exposures to airborne solid particles has been called into question largely because of the greater propensity of rats than of mice and Syrian hamsters to develop lung tumors after chronic exposures to dusts at high rates. The overloading of lung macrophage clearance itself does not render the rodent data irrelevant; the few data available suggest that particles can accumulate in heavily-exposed human lungs at concentrations similar to those observed in rodent bioassays. The finding of a lung cancer response in humans exposed heavily to particles would lend confidence to the extrapolation of the rodent carcinogenicity data, but there are few data allowing direct comparisons between humans and rodents of cancer responses to dust exposures. Although similar unit cancer risks for diesel exhaust exposures have been calculated for rats and estimated for humans, it is not clear if the mechanism by which the rat tumors develop would also occur in humans. The largest epidemiological data base on humans with heavy particle exposures comes from coal miners, but the existing rodent bioassay data for coal dust is not conclusive. Research is needed in three areas: 1) analysis of lung cancer data from all available heavily dust-exposed human populations; 2) comparison of the mechanisms by which lung tumors develop in humans and in animals exposed to dusts; and 3) conduct of a modern, dose-response inhalation bioassay in rats using dusts, such as coal, for which human lung cancer data exist. (Supported by the U.S. Department of Energy.)

2057358156

Assessment of the Potential Health Effects of Natural and Man-Made Fibres and Testing Needs: Perspectives of the U.S. Environmental Protection Agency

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The US Environmental Protection Agency (EPA) has recently added a "respirable fibres" category to the Master Testing List (MTL). EPA has been using the MTL since 1990 to set its chemical testing priorities. The concern for "respirable fibres" arises from findings that long, thin fibres of varying characteristics can cause diseases similar to those induced by asbestos. "Respirable fibres" are defined as man-made or naturally-occurring fibres (other than asbestos) with diameters less than 3.5 micrometers that can enter the small airways of the lower respiratory tract. A review of available information indicates that several of these fibres may present significant health risks while available data for other fibres are limited or inadequate. Hence, testing is needed to obtain necessary data to better characterize the potential health risks (toxicity and exposure), associated with the production and use of synthetic and naturally-occurring respirable fibres and products made from such fibres. Testing approaches to evaluate the carcinogenic and fibrogenic effects of inhaled fibres will also be discussed.

Source: https://www.industrydocuments.ucsf.edu/docs/hpgl0000

Current Approaches to Regulate Hazardous Substances Including Dusts at Work (EEC/FRG)

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Handling and use of hazardous substances at work is regulated in Germany by the Hazardous Substances Order (GefStoffV) and its subsidiary Technical Rules for Hazardous Substances (TRGS).

Traditionally the evaluations of the toxicity of substances by the Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK-Kommission) are taken over by the Committee on Hazardous Substances (AGS) as TRGS 900. It contains Maximum Concentrations at the Workplace (MAK-values), Biological Tolerance Values for Working Materials (BAT-values), an evaluation of embryotoxicity and/or fetotoxicity and a classification of carcinogens and mutagens. The classification of carcinogens and mutagens is based solely on the inherent carcinogenic or mutagenic hazard. No risk assessment is performed and no occupational exposure limits (OELs) are established.

For carcinogens and mutagens it is the task of the AGS to differentiate according to their respective potency and anticipated risks in handling and use (TRGS 910) and to assign a Technical Guiding Concentration (TRK-value, TRGS 102).

On an EEC level a directive for the classification and labelling of dangerous substances provides criteria for the "identification of all toxicological properties" (Directive 91/325/EEC). Principles for the handling of chemicals at work and protective measures are laid down in Directives 80/1107/EEC (amended by 88/642/EEC), 89/391/EEC and 90/394/EEC (carcinogens). They enable the establishment of European OELs, which is still in its beginning stage. For fine dust (alveolar dust) without any specific toxicity a general threshold limit value of 6 mg/m^3 is presently applied in Germany. It should prevent the impairment of respiratory organ function, which could result from the non-specific effects of dusts.

20573581S7

Notes

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Notes

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(as at 3rd February 1993)

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